REMARKS

Claim 8 has been amended to correct a typographical error. New claims 25-31 have been added. Support for these claims can be found in the claims as filed as well as in specification pages 5-10.

The final Office Action does not acknowledge or respond directly to the applicants' previous arguments. If the Office remains unpersuaded by the applicants' argument, the applicants respectfully request comments specifically explaining why.

Subsequent to the applicants' previously filed responses, the Supreme Court of the United States issued its ruling in *KSR Intern. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), addressing the legal standard for determining obviousness under 35 U.S.C. § 103 (the basis of all rejections on appeal). Accordingly, the applicants first discuss the KSR decision as a framework for addressing the present rejection.

Obviousness and *KSR Intern. Co. v. Teleflex Inc.*

In *KSR* the Court reaffirmed the objective standard set forth in *Graham v. John Deere Co. of Kansas City,* 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966):

> Under *§ 103*, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

While the Court rejected a rigid application of the so-called TSM test (teaching-suggestion-motivation) devised by the Federal Circuit, it acknowledged that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis. *KSR*, 127 S. Ct. at 1741; *see, also, Takeda Chem. Indus. v. Alphapharm Pty., Ltd.,* 2007 U.S. App. LEXIS 15349, 83 U.S.P.Q.2d 1169 (Fed. Cir. June 28, 2007). The Federal Circuit noted in *Takeda Chem. Indus.* that "[a]s long as the test is not applied as a 'rigid and mandatory' formula, that test can provide 'helpful insight' to an obviousness inquiry." 83 U.S.P.Q.2d at 1174. Thus,

the arguments presented in the applicants' Appeal Brief are still valid reasons why the claims on appeal are not obvious over the cited art.

In addition to the foregoing, the Court discusses additional factors to consider in the obvious analysis, recognizing that "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, 127 S. Ct. at 1741. But, reiterating prior holdings, the Court stated that merely identifying elements of an invention in the prior art is insufficient; more is required to establish obviousness. *Id.* ("As is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.")

The Court considered predictability as an important factor in the obvious analysis. In several instances the Court stated that a combination of elements may be obvious if their combination yielded a predictable result:

> The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. *Id.* at 1739 (emphasis added).
>
> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, *§ 103* likely bars its patentability. *Id.* at 1740 (emphasis added).
>
> [I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative -- a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. *Id.* (emphasis added).

As explained below, the prior art provides legally insufficient predictability in achieving the results of the invention claimed on appeal.

The Court also considered the forces driving innovation as important in the obvious analysis ("design incentives and other market forces can prompt variations of [a work]"):

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the

known elements in the fashion claimed by the patent at issue. *Id.* at 1740-41 (emphasis added).

> Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *Id.* at 1741 (emphasis added).

As explained more fully below, at the time the invention was made, there was little reason for one of ordinary skill in the art to make the present invention.

Other factors the Court reiterated as important in the obviousness analysis are teachings away from the claimed invention and the prohibition against hindsight reconstruction of it. "When the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). A teaching away is significant not only in itself, but because it may undermine any reason for making a claimed invention as well as diminish the predictability of any combination of prior art elements. As discussed below, the prior art provides a teaching away that does both.

And finally, the Federal Circuit recently confirmed that following *KSR* the law still requires that obviousness be established by demonstrating that the prior art provide reasons to make the particular invention and not merely general guidance. In *Pharmastem Therapeutics, Inc., v. Viacell, Inc.,* 2007 U.S. App. LEXIS 16245, *56; 83 U.S.P.Q.2d 1289, 1350 (Fed. Cir. 2007) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)), the court stated, "[A]n invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."

With the foregoing as guidance, the applicants respond to the pending rejection.

Rejection pursuant to 35 U.S.C. § 103

Claims 1 – 24 stand rejected under 35 U.S.C. § 103 as *prima facie* obvious over Chu, *et al., (2006.11.30) Office Action (final) ((2006.11.30)* Infection and Immunity, 40:245-56 (1983) (hereinafter "Chu *et al.*") in combination with Merck & Co. Inc., European Patent Application No. '525 A (hereinafter "EP '525").

Claim 1 recites a composition comprising at least two different kinds of polysaccharide-carrier protein conjugates, wherein the polysaccharide is derived from *Streptococcus pneumoniae* and wherein the carrier proteins of the conjugates are of at least two different types. Claims 2-15 and 24 are directly or indirectly dependent on claim 1, and therefore they also include these two claim elements. In the cited prior art, Chu fails to teach the second element (polysaccharide derived from *Streptococcus pneumoniae*), and while Chu teaches a composition comprising two carrier proteins, Chu fails to provide any teachings suggesting or motivating the use of two carrier proteins generally. Meanwhile, EP '525 fails to teach the first element (at least two conjugates comprising different carrier proteins). Therefore, to establish a *prima facie* case of obviousness, the Office must show some reason to combine the teachings of Chu and EP '525 to arrive at the composition recited in claim 1.

The Office has not identified any reason make any compositions in addition to those of Chu *et al.* comprising at least two different kinds of polysaccharide-carrier protein conjugates, wherein the conjugates contain different carrier proteins— let alone a reason make such a composition wherein the polysaccharide is derived from *Streptococcus pneumoniae*, as recited in claim 1. The Office has not shown that one of skill in the art would have a reason to modify the composition taught by Chu to arrive at the composition recited in claim 1. Nor has the Office identified anything in the prior art suggesting any advantages in employing different carrier proteins in the same vaccine composition that might provide a reason to make the claimed compositions.

In fact, upon reading the results described in Chu, one of skill in the art would have been discouraged from making any additional compositions comprising at least two different conjugates. This is because Chu's results of experiments with such compositions were actually negative—they failed to elicit a stronger immune response. As stated on page 249, col. 2, lines 8-17:

> The effect of injecting both Hib conjugates [*i.e.*, Hib-TT and Hib-HCH] was similar to that observed with the monovalent preparations. The total Hib polysaccharide dose was 2.5 μg in the mice receiving either the monovalent or the bivalent preparations. There were no differences between the anti-Hib antibodies in the groups that received both Hib conjugates after any of the three immunizations by using the criteria of either the GM or the percentage of responders.

Accordingly, Chu does not suggest that using two different carrier proteins has any beneficial or desirable effect. Indeed, the description of these results in Chu is tantamount to teaching away from making the composition recited in claim 1 because the ordinary artisan would have been discouraged from expending the extra effort of preparing such a composition knowing the concomitant uncertainties associated with adding extra antigenic components to such a composition. And as stated by the Federal Circuit, prior art references "must be read as a whole and consideration must be given where the references diverge and teach away from the claimed invention." *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986) (citing *W.L. Gore & Assocs. v. Garlock*, 721 F.2d 1540, 1550 (Fed. Cir. 1983)).

The final Office Action also stated: "Chu et al also teach that when Hib-HCH was injected with either Pn6A-HCH or Pn-TT [sic], both the anti-Hib and anti-Pn6A responses were increased over that induced by either conjugate alone." *See*, p. 3, lines 13-15. These results are irrelevant to the claims of this application because they involve two different non-pneumococcal polysaccharide antigens (claim 1) and two different non-Dt non-Tt carrier proteins (claim 16). Furthermore, it is unclear whether the results are due to there being two different antigens or two different carrier proteins in the composition, or whether there was some other reason for the observed increase. One simply cannot make any conclusion with regard to this observation and the presently claimed invention.

Moreover, if the results are due to there being two different carrier proteins, they contradict the results described above, where the Hib-HCH/Hib-TT combination was compared directly to either Hib-HCH or Hib-TT alone. Such contradictory evidence cannot rise to the level of suggesting the use of two carrier proteins.

Furthermore, the Office has not pointed to any reason supplied by EP '525 to modify the compositions taught therein to include more than one kind of carrier protein. EP '525 consistently describes compositions containing a single carrier protein. Neither has the Office offered any reason whatsoever that one would have been motivated to modify the compositions taught by EP '525 to arrive at the composition recited in claim 1. Thus, neither Chu nor EP '525, alone or in combination, provides the requisite suggestion or motivation to combine and/or modify their respective teachings to arrive at the presently claimed compositions.

An examination of the problems sought to be solved by Chu and by EP '525 reveals why each reference fails to suggest or motivate one to make the composition recited in claim 1. Both

Chu and EP '525 recognized that pure polysaccharides have limited use in vaccines because they do not produce a protective serum antibody response (*see*, *e.g.*, Chu at the paragraph bridging pp. 245-6). Accordingly, both research groups focused on the creation of new polysaccharide-carrier protein conjugates, including the development of new methods of making such conjugates, which elicit a stronger immune response than polysaccharide alone. However, neither Chu nor EP '525 noted the problem of "negative interference," which is a reduced immune response against a polysaccharide due to the maximum load of carrier protein having been reached. For this reason, neither Chu nor EP '525 sought to solve the problem of "negative interference" by creating a polysaccharide vaccine composition containing more than one carrier protein, as the applicant has done.

The Office's point that the simultaneous injection of two conjugates "did not exert a negative effect," as reported in Chu, is a red herring. *See* the final Office Action at p. 3, ll. 15-17. It is unclear from Chu *et al.* what the absence of a negative effect was due to. It could have simply been because a low dose of conjugate was administered—not because two different carrier proteins were used.

Furthermore, the Office's presumption of a motivation to combine Chu and EP '525 neglects the essential fact that vaccines are usually administered to healthy people. There is reluctance (rather than a motivation) to administer more than is necessary to a healthy person for fear of encountering unexpected adverse consequences. One would not combine antigens unless there is a reasonable expectation of achieving a beneficial result that outweighs any negative aspects. And in the field of immunology it is recognized that a combination of antigens does not necessarily result in a cumulative (let alone synergistic) response. Because of the phenomenon of antigenic competition (or negative interference, as mentioned above), whereby a combination of antigens results in a decreased immune response, one would not necessarily have expected to achieve a beneficial result (i.e., the results were not predictable).

Neither Chu nor EP '525 teaches or suggests an advantage of altering the compositions disclosed therein in any way; their compositions are already useful by themselves, as they are. In view of the reluctance of those skilled in the art to add additional components to a vaccine composition and the lack of any clear reason that making the modifications necessary to arrive at the presently claimed compositions would provide any beneficial effect, the requisite reason for making the claimed compositions is absent.

In addition, with regard to claims 16 et seq., these claims recite a composition comprising two different kinds of polysaccharide-carrier protein conjugates that differ in their carrier protein component, wherein one carrier protein is diphtheria toxoid (Dt) and the other carrier protein is tetanus toxoid (Tt). Claims 16-23 are directly or indirectly dependent on claim 16, and therefore they also include these two claim elements as do new claims 25-31.

Chu fails to teach or suggest Dt as a carrier protein, while EP '525 fails to teach or suggest at least two conjugates comprising different carrier proteins. To establish a *prima facie* case of obviousness, the Office must show some reason to combine the teachings of Chu and EP '525 to arrive at the composition of claim 16-31.

As noted above, the Office has not pointed to any reason in Chu or EP '525 to make any additional compositions comprising at least two different kinds of polysaccharide-protein conjugates, wherein the conjugates contain different carrier proteins—including those comprising Dt carrier protein, as recited in claim 16. Moreover, as was the case with claim 1, the Office has not shown that one of skill in the art would have a reason to modify the composition taught by Chu to arrive at the composition recited in claim 16. Again, upon reading the negative results reported in Chu, one of skill in the art would have been discouraged from making any additional compositions comprising at least two different conjugates. *See* Chu at page 249, col. 2, lines 8-17.

As was the case with claim 1, the reasons offered by the Office for why one would have been motivated to modify the compositions taught by Chu, thereby arriving at the composition recited in claim 16, are legally insufficient. For example, at p. 4, ll. 24-27, the Office stated: "it would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to substitute the protein Dt of Merck and Co Inc for the HCH in the Hib-HCH conjugate of Chu et al because Chu et al teach that a 'useful' carrier would be preferred in human use . . . ." Even assuming that Dt is a "useful" carrier (it is not described as such in Chu), this argument completely ignores the point made above: the results reported by Chu discourage one from making any additional compositions comprising more than one carrier protein—regardless of whether Dt is one of the carrier proteins included in the composition.

Furthermore, as noted above with regard to claim 1, the Office has not pointed to any reason provided by EP '525 to modify the compositions taught therein to include more than one kind of carrier protein; EP '525 consistently describes compositions containing a single carrier

protein. In addition, the Office has not offered any reason to modify the compositions taught by EP '525 to arrive at the composition recited in claim 16 et seq.. EP '525 was cited simply as a secondary reference—one that merely describes the use of Dt in a *Streptococcus pneumoniae* vaccine composition.

Because neither Chu nor EP '525 provide any reason to combine their teachings to arrive at the compositions recited in the claims, a *prima facie* case of obviousness has not been established with respect to these claims. For this reason as well, the applicant respectfully requests withdrawal of this obviousness rejection.

CONCLUSION

With the above amendments and remarks, the Applicant respectfully submits that the application is in condition for allowance. If the Examiner is of the opinion that a telephone conference would expedite prosecution of this matter, the Examiner is encouraged to contact the Applicant's undersigned representative.

Respectfully submitted,

Date: December 27, 2007

/Michael S. Greenfield/
Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002